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ORIGINAL ARTICLE

Resting energy expenditure and its determinants in hemodialysis patients

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Objective: Chronic kidney disease is associated with several metabolic disturbances that can affect energy metabolism. As resting energy expenditure (REE) is scarcely investigated in patients on hemodialysis (HD) therapy, we aimed to evaluate the REE and its determinants in HD patients.
Design: Cross-sectional study.
Setting: Dialysis Unit of the Nephrology Division, Federal University of São Paulo, Brazil.
Subjects: The study included 55 patients (28 male, 41.4 ± 12.6 years old) undergoing HD therapy thrice weekly for at least 2 months, and 55 healthy individuals pair matched for age and gender. Subjects underwent fasting blood tests, as well as nutritional assessment, and the REE was assessed by indirect calorimetry.
Results: REE of HD patients was similar to that of pair-matched controls (1379 ± 272 and 1440 ± 259 kcal/day, respectively), even when adjusted for fat-free mass ($P = 0.24$). REE of HD patients correlated positively with fat-free mass ($r = 0.74$; $P < 0.001$) and body mass index ($r = 0.37$; $P < 0.01$), and negatively with dialysis adequacy ($r = -0.46$; $P < 0.001$). No significant univariate correlation was found between REE and age, dialysis vintage, serum creatinine, urea, albumin, bicarbonate, parathyroid hormone (PTH) or high-sensitivity C-reactive protein (CRP). In the multiple linear regression analysis, using REE as dependent variable, the final model showed that besides the well-recognized determinants of REE such as fat-free mass and age, PTH and CRP were the independent determinants of REE in HD patients ($R^2 = 0.64$).
Conclusions: In this study, the REE of HD patients was similar to that of healthy individuals, even with the positive effect of secondary hyperparathyroidism and inflammation on REE of these patients.
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Introduction

Resting energy expenditure (REE) is the major component of human total energy expenditure accounting for 60–75% of variations (Institute of Medicine/Food and Nutrition Board, 2002). The determination of REE is important for the establishment of energy recommendations and maintenance of nutritional balance of the individuals (Cuppari and Avesani, 2004). Elevated REE has been pointed out as a contributory factor for cachexia in several disease conditions (Riley *et al.,* 1991; Falconer *et al.,* 1994) and an association with mortality has been suggested (Wang *et al.,* 2004). However, little is known about REE and its determinants in chronic kidney disease (CKD) patients undergoing hemodialysis (HD). Actually, few studies have evaluated the REE of dialysis patients. Two decades ago, Monteon *et al.* (1986) have first examined the REE of chronic HD patients showing that REE was not different from that of healthy controls. Ten years later, however, a study by Ikizler *et al.* (1996) reported a significant increased REE in HD patients (15–20% during

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dialysis session and 7.5% in the interdialytic day) compared with control subjects. Uremia *per se* and the dialysis procedure are associated with some metabolic derangements such as metabolic acidosis, insulin resistance and inflammation, that augment protein catabolism (Mitch *et al.,* 1999) and could in turn contribute to the variations of REE. Accordingly, it has been shown that nondialysis CKD patients with poorly controlled diabetes (Avesani *et al.,* 2001) and HD patients with severe hyperparathyroidism (Cuppari *et al.,* 2004) have increased REE. Inflammation is a highly prevalent condition among CKD patients. Cross-sectional studies have shown that 30–50% of nondialysis (Ortega *et al.,* 2002) and dialysis (Docci *et al.,* 1990; McIntyre *et al.,* 1997) patients present serologic evidence of an activated inflammatory response with elevated serum concentration of C-reactive protein (CRP). Our group has recently reported increased REE in nondialysis patients with CRP > 0.5 mg/dl (Avesani *et al.,* 2004a). When we extended our investigation into the relationship among infection, inflammation and REE, it was shown that after treatment of infection/inflammation a significant decrease in CRP was accompanied by a 13% reduction of REE (Utaka *et al.,* 2005).

If on the one hand HD patients are exposed to several catabolic conditions that may directly affect REE, on the other renal failure might be associated with hypometabolic state owing to altered cell metabolism (Om and Hohenegger, 1980) and lower oxygen consumption by the kidney (Kurnik *et al.,* 1992). Thus, considering that the factors affecting REE of HD population are not fully understood, we aimed to compare the REE of HD patients with that of pair-matched healthy individuals, and to evaluate the determinants of REE in these particular patients.

Subjects and methods

Patients

Patients were recruited from the Dialysis Unit of the Federal University of São Paulo (São Paulo, SP, Brazil). Fifty-five HD patients (28 men and 27 women) older than 18 years, without altered thyroid function and/or presence of malignance, were included in the study protocol. Diabetes was an exclusion criterion; however, two well-controlled diabetic patients with normal serum glucose level were included. Patients were dialyzed 4 h thrice weekly for at least 2 months. The majority of the patients were using iron saccharate and vitamin complex and none was using hormone, corticosteroid or immunosuppressive drugs. The selected patients were gender and age pair matched (matching limits for age were ± 3 years) with a group of 55 healthy individuals. Control subjects, most of them clinic employees, had normal renal and thyroid functions, and none was taking medication.

The study was approved by the University Ethical Advisory Committee and all subjects gave informed consent.

Study design and protocol

In this cross-sectional study, the REE of HD patients was compared to that of control subjects. In the HD group, the indirect calorimetry and blood tests were carried out on interdialytic day, whereas nutritional assessment was performed postdialysis session (15–30 min) in the day before the calorimetry. Control group underwent fasting blood tests, as well as nutritional assessment, in the same day of the indirect calorimetry test.

Anthropometry and body composition

Subjects were weighed with light clothes and without shoes on a platform manual scale balance (Filizola, São Paulo, Brazil). Body mass index (BMI) was calculated as body weight divided by squared height. Fat-free mass and body water were assessed by bioelectrical impedance analysis using a single-frequency tetrapolar technique with an electrical current of 800 μA at 50 kHz (BIA 101 Quantum, RJL Systems, Detroit, MI, USA). The electrodes were placed in the standard positions (two electrodes placed on the hand and wrist and another two positioned on the foot and ankle) in the opposite side of vascular access, with the subject in supine. The software Fluids & Nutrition (version 3.0), (RJL Systems, USA) provided by the manufacturer was used to estimate the fat-free mass and body water.

Skinfold measurement at four standard sites (biceps, triceps, subscapular and suprailiac) was performed for determining body fat, as the method seems to be superior to bioelectrical impedance analysis for the measurement of this compartment (Kamimura *et al.,* 2003). Body density was calculated from the sum of the four skinfold measurements according to Durnin and Womersley (1974), and the percentage of body fat was then calculated by Siri's (1961) equation.

Resting energy expenditure

REE measurements were obtained by indirect calorimetry using an open-circuit ventilated computerized metabolic system (Vmax series 29n; SensorMedics Corp; Yorba Linda, CA, USA). The oxygen and carbon dioxide sensors were calibrated before each REE measurement with the use of mixed reference gases of known composition. All subjects were previously instructed to refrain from any unusual physical activity 24 h before the test and to sleep at the same time as usual in the night before the REE measurement. They were admitted in the clinic at 08:00 after an overnight fast of 12 h. After resting for 30 min in a recumbent position, subjects breathed for 30 min through a clear plastic canopy over their heads in a quiet dimly lit thermo neutral room. They were instructed to avoid hyperventilation, fidgeting or falling asleep during the test. Oxygen consumption and carbon dioxide production were measured at 1-min intervals and the mean of the last 20 min were used to calculate the REE according to the Weir's equation without using urinary

urea nitrogen (Weir, 1949). The intra-individual variation coefficient for REE was 5%.

Laboratory data

In the HD group, serum creatinine and urea were obtained from the monthly routine examination. Blood samples for glucose, bicarbonate, thyroid stimulating hormone (TSH), serum albumin, intact parathyroid hormone (PTH) and high-sensitivity CRP were drawn just before the indirect calorimetry test. The control group had serum determination of creatinine, glucose, TSH and CRP also before the indirect calorimetry test.

Serum creatinine, urea and glucose were determined using a standard autoanalyzer. Bicarbonate was measured by an automated potentiometer (normal range: 23–27 mmol/l), TSH by immunofluorometric assay (normal range: 0.3–4.0 μIU/ml), and serum albumin by green bromcresol method (normal range: 2.5–4.0 g/dl). Intact PTH and high-sensitivity CRP (inflammatory state: $\geqslant$0.5 mg/dl) were determined by immunochemiluminescence. Dialysis adequacy was assessed by Kt/V (adequate dialysis Kt/V > 1.2) as recommended by the National Kidney Foundation guideline (2001).

Statistical analysis

Data are expressed as mean $\pm$ standard deviation or median and ranges according to the variable distribution. For comparisons between the HD group and the control group, the two-tailed paired Student's t-test and χ^2 test were used, as appropriate. Pearson's or Spearman's univariate analysis was used to identify the variables that correlated with REE. In order to evaluate the factors affecting REE among HD patients, stepwise multiple linear regression analysis was applied including those variables that correlated significantly with REE or those that might influence REE. As the use of ratios for adjusting REE for fat-free mass may create errors and differences between the two groups may be found when there is no actual difference (Ravussin and Bogardus, 1989), for the comparison of REE between the two groups REE was adjusted for fat-free mass using multiple linear regression analysis with robust estimation for the error structure owing to the matching design of the study (Kleinbaum *et al.*, 1998). Differences with $P<0.05$ were considered statistically significant. The statistical analyses were conducted using the True Epistat software (Texas, USA, 1995) and Stata Corp software, release 7.0 (TX, USA, 2001).

Results

Demographic, clinical and laboratory characteristics of the subjects are provided in Table 1. The age of patients ranged from 19 to 75 years, and the vintage on dialysis therapy ranged from 2 months to 13 years. Patients were receiving adequate dialysis dose according to the Kt/V. All subjects had normal thyroid function. The main etiology of CKD was hypertensive nephrosclerosis (35%), followed by undetermined causes (31%), chronic glomerulonephritis (11%), interstitial nephritis (7%) and others (16%). As expected, HD patients exhibited higher levels of CRP in comparison to control subjects. Increased CRP levels (defined as CRP $\geqslant$0.5 mg/dl) were found in 43.6% of the patients. On the other hand, patients had lower BMI, body fat and fat-free mass. REE adjusted for fat-free mass did not differ between HD patients and healthy individuals (Figure 1).

In the HD group, REE correlated positively with fat-free mass ($r=0.74$; $P<0.001$) and BMI ($r=0.37$; $P<0.01$), and negatively with Kt/V ($r=-0.46$; $P<0.001$). No significant correlation was found between REE and age, dialysis vintage,

Table 1 Demographic, clinical and nutritional characteristics of the subjects

	HD group (n = *55*)	*Control group* (n = *55*)	P-*value*
Gender (male/female)	28/27	28/27	
Age (years)	41.4 $\pm$ 12.6	41.5 $\pm$ 12.5	0.80
Length of dialysis (months)	34.5 $\pm$ 33.6	—	
Kt/V	1.36 $\pm$ 0.2	—	
Serum creatinine (mg/dl)	10.9 $\pm$ 3.2	0.9 $\pm$ 0.2	<0.001
Blood urea nitrogen (mg/dl)	72.9 $\pm$ 15.8	—	
Serum glucose (mg/dl)	92 $\pm$ 79	82.6 $\pm$ 16.3	0.37
PTH (pg/ml)[a]	166.3 (1–2154)	—	
TSH (μIU/ml)	2.1 $\pm$ 2.2	1.56 $\pm$ 0.92	0.21
Serum bicarbonate (mmol/l)	23.0 $\pm$ 4.25	—	
Serum albumin (g/dl)	4.1 $\pm$ 0.5	—	
CRP (mg/dl)[a]	0.45 (0.01–15)	0.11 (0.02–2.48)	<0.001
BMI (kg/m^2)	22.5 $\pm$ 2.5	25.1 $\pm$ 3.8	<0.001
Body fat (kg)	14.1 $\pm$ 5.4	19.4 $\pm$ 6.3	<0.001
Body water (%)	54.1 $\pm$ 4.9	52.9 $\pm$ 5.8	0.12
Fat-free mass (kg)	44.9 $\pm$ 9.7	50.1 $\pm$ 10.7	<0.001
REE (kcal/day)	1379 $\pm$ 272	1440 $\pm$ 259	0.11

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HD, hemodialysis; PTH, parathyroid hormone; REE, resting energy expenditure; TSH, thyroid stimulating hormone.
Values given as mean and $\pm$standard deviation.
[a]Median and range.

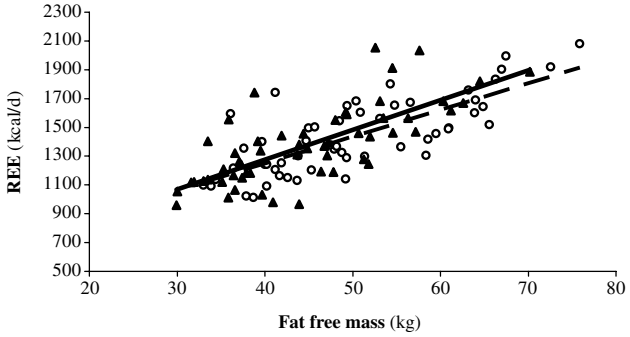

Figure 1 REE in relation to fat-free mass in HD group (▲—) and control group (○– –). Coefficient −40.8 ($P=0.24$), confidence interval −109.7 to 28 kcal.

serum creatinine, urea, albumin, bicarbonate, PTH or CRP. As expected, a negative correlation was found between CRP and albumin ($r=-0.36$; $P<0.01$). A direct association of CRP with age was observed ($r=0.36$; $P<0.01$); however, no correlation was found between CRP and other laboratory or nutritional parameters. In the multiple linear regression analysis using REE as dependent variable, the final model showed that age, fat-free mass, CRP and PTH were the independent determinants of REE in HD patients (Table 2).

Discussion

This study showed that REE of HD patients was comparable to that of age and gender-matched healthy controls. This finding is in accordance with some investigators (Monteon *et al.,* 1986; Schneeweiss *et al.,* 1990), but differs from others who found increased REE in HD patients (Ikizler *et al.,* 1996). The exact factors affecting REE of CKD patients are not fully understood, but several mechanisms involving HD patients may lead to either increase or reduction of REE.

Kidneys have important metabolic functions and perform a number of oxygen-dependent activities (Silva, 1987). In healthy individuals, the kidneys account for up to 20% of the REE (Wang *et al.,* 2004). Hence, renal failure might be associated with decrease in energy metabolism. In fact, Kurnik *et al.* (1992) have demonstrated that patients with moderate loss of renal function have lower renal blood flow and lower renal oxygen consumption per kidney than healthy individuals. Moreover, the profound abnormalities in cell metabolism that occur in renal failure (Om and Hohenegger, 1980) and the impaired energy metabolism of skeletal muscle caused by circulating uremic toxins (Conjard *et al.,* 1995) may be additional factors contributing to reduce REE in renal failure patients. Accordingly, studies with CKD patients not yet on dialysis have recently demonstrated lower REE than healthy pair-matched controls (O'Sullivan *et al.,* 2002; Avesani *et al.,* 2004b). In HD patients evaluated in a nondialysis day, a recent study showed that protein breakdown and oxidation was considerably reduced compared with control subjects, suggesting lower metabolic activity in this patient group (Veeneman *et al.,* 2004). However, REE was not assessed in that study.

Table 2 Multiple linear regression analysis using REE as dependent variable in HD group ($R^2=0.64$)

	Coefficient (kcal)	P-*value*	*95% CI*
Age	−5.7	<0.01	−9.35 to −2.04
Fat-free mass	20.6	<0.0001	16 to 25.2
PCR	23.6	<0.01	6.4 to 39.7
PTH	0.13	0.02	0.03 to 0.23
Constant	613.5		

Abbreviations: CI, confidence interval; HD, hemodialysis; PTH, parathyroid hormone.

In contrast to the possibilities described above, the comorbid conditions commonly present in CKD are important contributors for elevating REE in HD patients. The multiple regression analysis showed that besides the well-known determinants of REE such as fat-free mass and age, CRP and PTH were also independent determinants of REE in HD patients. Inflammation is frequent among CKD patients and is a powerful predictor of mortality in dialysis patients (Zimmermann *et al.*, 1999). It has been suggested that low clearance of CRP and cytokines, uremia itself, hypervolemia and the presence of comorbidities are possible causes for inducing the acute-phase reaction in dialysis patients (Stenvinkel and Yeun, 2004). We found that 43.6% of the patients ($n=24$) had CRP levels of 0.5 mg/dl or greater, a value considered indicative of an inflammatory condition. A direct association between inflammatory state and REE has been reported in other disease conditions such as rheumatoid arthritis (Roubenoff *et al.,* 1994), acquired immune deficiency syndrome (Garcia-Lorda *et al.,* 2000), sepsis (Chioléro *et al.,* 1997) and pancreatic cancer (Falconer *et al.,* 1994). Recently, our group also demonstrated such relationship in CKD patients not yet on dialysis (Avesani *et al.,* 2004a; Utaka *et al.,* 2005). To the best of our knowledge, this is the first study that evaluated the association of REE and inflammation in patients undergoing HD therapy. The exact mechanisms involving inflammation and REE cannot be fully identified, but it seems reasonable to speculate that protein catabolism caused by inflammation might be implicated in the increase of REE. In fact, our HD patients exhibited elevated CRP and reduced fat-free mass when compared to pair-matched healthy controls. Actually, the association of elevated inflammatory markers and reduced muscle mass measured by computed tomography has been observed in HD patients (Kaizu *et al.,* 2003). We failed to show such correlation in our study. However, the low sensitive method used for assessing fat-free mass and the cross-sectional design of this study could be implicated in the lack of association between CRP and muscle mass. Another potential catabolic factor, related or not to the inflammatory process, is the HD procedure *per se*. A recent study showed that rates of both whole body and, more intensively, muscle proteolysis were significantly increased during HD (Ikizler *et al.,* 2002). In the same study, the authors found a significant increase in energy expenditure during the dialysis session and in the subsequent 2 h when compared to basal (7 and 12%, respectively), suggesting that because protein synthesis and breakdown are processes that require energy, part of this energy increase may be due to the increased protein turnover. The fact this catabolic event is less exacerbated in a nondialysis day (Veeneman *et al.,* 2004) could explain the finding of non-increased REE found in the current study, in which REE was obtained in an interdialytic period.

High PTH levels have been demonstrated to be associated with reduced fat-free mass and increased REE in chronic HD patients (Cuppari *et al.,* 2004). In this recent study, patients

with severe hyperparathyroidism (defined as PTH $\geqslant$700 pg/ml) showed markedly increased REE when compared to patients with lower values of PTH and healthy controls pair matched for age and gender. Additionally, after parathyroidectomy REE decreased significantly (23.1%). PTH excess has been pointed as exerting toxic effects on various organs and body systems. Besides bone, several lines of evidence indicate that skeletal muscle is also a target organ for PTH. It has been documented that excessive PTH affects the bioenergetics of skeletal muscle, impairing energy production, transfer and utilization (Baczynski *et al.,* 1985). In addition, the hormone may enhance muscle proteolysis and increase the release of alanine and glutamine *in vitro* (Garber, 1983). If we consider that protein catabolism by circulating PTH may contribute to elevate REE in these patients, then an association of PTH with muscle parameter would be expected. However, in our patients no correlation of PTH with fat-free mass was found. The lack of association between them could be in part explained by the predominance of patients with lower PTH observed in our sample, 27 patients (49%) had PTH $<$200 pg/ml, and other 19 (34.5%) had mild to moderate levels of PTH (defined as PTH 200–700 pg/ml), and only nine patients had excessive PTH. Finally, although PTH and CRP were determinants of REE in the current study, it is possible that their levels were not sufficient to determine REE higher than those of controls.

In conclusion, HD patients yielded similar REE with that of healthy pair-matched controls. Moreover, we demonstrated that besides the well-recognized determinants of REE such as fat-free mass and age, frequent condition in CKD such as secondary hyperparathyroidism and inflammation were positively associated with REE. As HD patients present concomitant factors, particular to the disease and the dialysis procedure, that contribute to both reduction and elevation of REE, further studies are necessary to evaluate the hypometabolic and hypermetabolic conditions involving patients on HD therapy.

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